URINARY TRACT INFECTIONS
Recurrent Urinary Tract Infections in Adults: Antibiotic Prophylaxis

Definition
The symptoms of a lower urinary tract infection include frequency, dysuria, urgency and suprapubic pain. Recurrent lower urinary tract infection (rUTI) is defined as:

Two or more episodes of lower urinary tract infection in the last 6 months, or
Three or more lower urinary tract infection episodes in the last 12 months[1].

It does not include bacteriuria in the absence of symptoms or catheterised patients, i.e., asymptomatic bacteriuria. Asymptomatic bacteriuria should not be screened for or treated unless prior to urological surgery or in pregnancy (positive cultures in pregnancy should be confirmed with a second culture confirming the same organism prior to treatment)[2].

1. Consider referral for patients with recurrent UTIs:

Red Flags for Referral to Urology[1,3]:
- All men, trans women and non-binary people with a male genitourinary system.
- Frank haematuria, even in the context of confirmed UTI
  (refer to current '2 week wait' guidelines for further information).
- Neurological disease e.g., spinal cord injury, spina bifida.
- Prior abdominopelvic malignancy.
- Pneumaturia or faecaluria.
- Proteus on repeat urine cultures.
- Suspected stone.
- Obstructive symptoms, known structural/functional abnormality (including previous urinary tract surgery pelvic organ prolapse surgery or trauma), OR any of the following features are present on renal ultrasound:
  - Hydroureter or hydronephrosis,
  - Bladder OR ureteric OR obstructive renal stones (for non-obstructive renal stones please use advice and guidance),
  - Post-micturition residual volume greater than 150ml.

In pregnancy:
- All recurrent UTIs in pregnancy should be discussed with the Obstetrics team.

Consider whether referral or specialist advice is required for the following factors:
- Recurrent upper UTI (or recurrent lower UTI if unknown underlying cause)
- Suspected cancer, in line with NICE's guideline on suspected cancer: recognition and referral
- Gender reassignment surgery involving structural alteration of the urethra

If concerns persist, or symptoms remain uncontrolled despite optimal primary care management, for non-pregnant females, trans men and non-binary people with a female urinary system who do not meet the above criteria for specialty referral (including those with recurrent UTI if unknown underlying cause), primary care clinicians should use 'advice and guidance' to seek specialist advice in the first instance, prior to referral.

Consider risk factors:
Sexual history and investigations for sexually transmitted infections should be performed if appropriate. In peri- and post-menopausal women, trans men and non-binary people with a female urinary system atrophic vaginitis may cause urinary symptoms and may increase the risk of bacteriuria. Due to low oestrogen levels

in post-menopausal women, trans men and non-binary people with a female urinary system with recurrent UTIs, consider using intravaginal oestrogens[4].

Microbiological Confirmation:

Patients with rUTIs should have a mid-stream urine (MSU) sample sent for culture before antibiotics are initiated to confirm infection and guide antibiotic therapy[3]. Patients should be counselled on how to provide a specimen to minimise the chance of contamination.

http://patient.info/health/midstream-specimen-of-urine-msu

In symptomatic patients with pyuria and a negative culture who do not respond to antibiotics as expected, consider whether an alternative diagnosis may be relevant. Sterile pyuria can occur in a number of infective conditions, including sexually transmitted diseases (e.g., Chlamydia), infections with organisms that are difficult to grow on standard culture, and renal tuberculosis, as well as non-infectious causes.

It is important to note that a negative urine culture in symptomatic patients with pyuria does not rule out infection[5]. Symptomatic patients with persistent sterile pyuria (persistent presence of white blood cells in the urine that repeatedly do not grow any organisms on routine culture) and symptoms strongly suggestive of urinary tract infection should be discussed with the duty microbiologist.

Urine cultures sent in the absence of symptoms are unlikely to be helpful, may detect asymptomatic bacteriuria and lead to inappropriate antibiotic use. Antibiotic treatment of asymptomatic bacteriuria is more likely to be harmful than beneficial[4].

'Clearance' cultures are not recommended if symptoms have resolved.

2. Management of Initial Presentation of Recurrent UTI in non-pregnant females trans men and non-binary people with a female urinary system - see flow chart

The following conservative measures may be advised however, the evidence is poor quality or inconclusive:

Conservative Measures:

- Drink plenty
- Avoid use of scented washes/wipes
- For sexually active women, trans men and non-binary people with a female urinary system:
  - Advise post-coital voiding
  - Avoid use of contraceptive diaphragm and spermicide
- Perineal hygiene i.e., wiping front to back.
- Avoid using flannels. A clean unscented disposable wipe is preferable.
- Over-the-counter products – limited evidence but some women, trans men and non-binary people with a female urinary system may find useful:
  - D-mannose (1g twice daily. Available without prescription)
  - Cranberry tablets (Follow individual product instructions. Available without prescription. Contraindicated in patients on Warfarin)[6]

Recurrent UTI Prophylaxis Prescribing Strategies

The relative risks and benefits of the following recurrent UTI prophylaxis prescribing strategies should be discussed with the patient. These strategies should be in addition to the conservative measures detailed above and are based on the patient's history and risk factors.

Summary of Prescribing Strategy Options	
Vaginal Oestrogen	Consider prescribing a vaginal oestrogen in peri- and post-menopausal women, trans men and non-binary people with a female urinary system.
Single-dose Antibiotic (one-off dose)	For rUTIs due to an identifiable trigger (e.g. sexual intercourse).
Continuous Urinary Antiseptic Prophylaxis	Continuous prophylaxis with methenamine hippurate as an initial alternative to continuous antibiotic prophylaxis. **Consider methenamine hippurate as an initial alternative to avoid use of antibiotics if recurrent UTI has not been adequately improved by (if applicable and appropriate):** **• vaginal oestrogen,** **or** **• single-dose antibiotics.**
Continuous Antibiotic Prophylaxis	Continuous low-dose antibiotic prophylaxis.
Standby Antibiotics	A 'self-start' course of antibiotics if <1 episode per month.

- **Vaginal Oestrogen**
  - Off-label use
  - Consider vaginal oestrogen for recurrent UTI if behavioural and personal hygiene measures alone are not effective or not appropriate.
  - When discussing vaginal oestrogen for preventing rUTIs, cover the following to ensure shared decision making:
    - → severity and frequency of previous symptoms,
    - → risk of developing complications from rUTIs,
    - → possible benefits of treatment, including for other related symptoms i.e. vaginal dryness,
    - → that serious side effects are very rare.
    - → that vaginal oestrogen is absorbed locally – a minimal amount is absorbed into the bloodstream, but this is unlikely to have a significant effect throughout the body.
    - → the person's preferred option for treatment and in line with local formulary (e.g. a cream, gel, tablet, pessary or ring). These can be added alongside systemic HRT which does not protect against UTIs.
  - Review use of vaginal oestrogen within 12 months, or earlier if agreed with the person.
  - Do not offer systemic hormone replacement therapy specifically to reduce risk of rUTIs.

Available topical oestrogen options:

Vaginal oestrogen formulation	Dose	Contraindications, cautions and monitoring
Intravaginal creams & gels **Estriol 0.1%** (1mg/g) **cream (preferred strength and most cost-effective option)**	Apply 1 applicatorful daily for 3–4 weeks, then reduced to 1 applicatorful twice weekly, to be applied at bedtime.	• Estriol vaginal cream, Estradiol pessaries or vaginal tablets, and *Estring*® vaginal rig are used for the prophylaxis of recurrent urinary-tract infection in postmenopausal women but are not licensed for this indication. • Ensure prescription is reviewed 12 monthly • Contraindications: ○ Active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction) ○ history of breast cancer, oestrogen-dependent cancer, ○ history of VTE or thrombophilic disorder
Vaginal Tablets/Pessaries **Estradiol 10micrograms vaginal tablets** (Prescribe generically. Pessaries are for 2nd line use if vaginal cream isn't suitable.)	10 micrograms daily for 2 weeks, then reduced to 10 micrograms twice weekly.	
Vaginal Ring		

Estradiol 7.5mcg/24hr (Estring®)	To be inserted into upper third of vagina and worn continuously; replace after 3 months.	○ undiagnosed vaginal bleeding or untreated endometrial hyperplasia • Cautions: see BNF entries for estriol and estradiol.

- **Single-dose Antibiotic (one-off dose)**
  - This can be considered for women, and trans men and non-binary people with a female urinary system, who are not pregnant for rUTIs due to an identifiable trigger.
  - For rUTIs triggered by sexual intercourse, this strategy is as effective as continuous antibiotic prophylaxis[7] and reduces antibiotic exposure and the risk of resistance emerging as well as adverse effects encountered.

- **Continuous Urinary Antiseptic Prophylaxis (Methenamine hippurate)**
  - Methenamine hippurate is a urinary antiseptic agent that is converted to formaldehyde in an acidic urine environment which is directly toxic to bacteria.
  - A randomised control trial in 2022 demonstrated methenamine hippurate was non-inferior to prophylactic antibiotics for reducing the incidence of symptomatic UTIs over a 12-month period[8] and its use limits the risks of long-term prophylactic antibiotic treatment, including resistance and adverse effects such as *C. difficile* infection.
  - Methenamine should be offered as an initial alternative to continuous antibiotic therapy for UTI prevention in women, trans men and non-binary people with a female urinary system. It may be initiated in primary care in women, trans men and non-binary people with a female urinary system without urinary tract abnormalities or neuropathic bladder (Amber 3 classification).
  - Methenamine should **NOT** be used for the treatment of UTIs.
  - There is suggestion that methenamine works in an acidic urine environment however the effectiveness of urine pH testing has not been explored, so the value of routine dipstick testing is currently not advised in this guideline.
  - Seek specialist advice if considering methenamine hippurate as an alternative to daily antibiotic prophylaxis for recurrent UTI:
    → during pregnancy.
    → in people with recurrent upper UTI or complicated lower UTI,
    → in men, and trans women and non-binary people with a male genitourinary system.
  - The use of methenamine hippurate as prophylaxis for recurrent upper UTI or complicated lower UTI is recommended by NICE but is off label.
  - If discussing methenamine hippurate as a preventative treatment, explain that:
    - Over-the-counter sachets that make urine more alkaline (e.g. those that contain potassium citrate or sodium citrate) should not be used while taking methenamine hippurate because these can make the medicine less effective.
    - Medical help should be sought for acute UTI symptoms.

- **Continuous Antibiotic Prophylaxis**
  - Continuous antibiotic prophylaxis is strongly associated with the development of antimicrobial resistance.
  - A **6-month trial** of a low-dose nightly antibiotic may be beneficial if rUTIs are occurring ≥1 per month and are not triggered by sexual intercourse.
  - Patients should be counselled at an early stage that antibiotic prophylaxis is not usually a lifelong treatment. Documenting and triggering a review date in the patient's record and on the repeat

prescription is recommended to avoid prolonged courses of antibiotics without review.

- **Standby Antibiotics**
  - There is no evidence from systematic reviews and RCTs for using a course of antibiotics to keep at home for treating an acute UTI in people with rUTIs (also known as stand-by antibiotics).
  - The use of stand-by antibiotics could potentially lead to inappropriate antibiotic overuse in the absence of medical supervision, however, may limit antibiotic exposure if used appropriately in certain cases.
  - This option could be considered for patients with <1 UTI per month (as could limit antibiotic exposure and risk of resistance emerging). A Patient Advice Sheet and boric acid container for pre-antibiotic MSU should be provided to the patient. A urine specimen should be obtained when the patient becomes symptomatic, but patients can self-initiate antibiotics whilst awaiting the culture results.
  - Prescribe a 'self-start' antibiotic according to previously known sensitivities and choose the narrowest spectrum agent available[9]. Refer to Nottinghamshire APC Antibiotic Guidelines for more information.
  - Safety-net with advice to seek medical attention if they develop fever, loin pain, or symptoms are not improving by 48 hours.

Choice of Agents for Prophylaxis[6,10]:

The choice of agent should be based on patient preference, consideration of the patient's co-morbidities, renal function and any contra-indicating factors.

If prescribing antibiotics, the choice of antibiotic should be based on **confirmed culture and sensitivity results** (wherever possible). The antibiotics licensed for the prophylaxis of UTIs are trimethoprim and nitrofurantoin.

The risk of adverse effects (see box below), as well as common side-effects such as rashes, oral/vaginal thrush, and gastrointestinal upset, should be discussed with the patient.

Methenamine as an initial alternative to continuous antibiotic prophylaxis

Antiseptic	Dose	Cautions and Monitoring
Methenamine	1 g twice a day	• Check baseline LFTs, U&Es and eGFR. • Not for the treatment of UTI. • Avoid in patients with a history of febrile UTI or previous urosepsis. • Contra-indications: Gout, metabolic acidosis, severe dehydration. • Renal impairment: Avoid if eGFR <10ml/min. • Hepatic impairment: Avoid. • Pregnancy: Preferable to avoid as inadequate evidence of safety. • Uncommonly can cause epigastric discomfort and skin reactions.

OR

First-line antibiotic options

Antibiotic	Dose	Cautions and Monitoring
Trimethoprim	200 mg one dose post-coital (off-label)	• Hyperkalaemia: caution when prescribing medications such as spironolactone, ACE inhibitor or angiotensin inhibitors. • Renal Impairment: Avoid if eGFR <15ml/min.

	or 100 mg nightly	Discuss with a renal physician if eGFR <30ml/min. It may increase serum creatinine. • Patients should be counselled on the risk of blood disorders and advised to seek attention if fever, sore throat, purpura, mouth ulcers, bruising or bleeding occurs.

OR

Nitrofurantoin	100 mg immediate release one dose post-coital (off-label) Or 50 mg nightly	• Avoid if renal function eGFR <45ml/min. Consider checking renal function prior to commencing continuous prophylaxis, especially in the elderly. • Avoid if G6PD deficiency. • Use with caution in anaemia, diabetes, vitamin B or folate deficiencies. • Monitor full blood count, renal function, and liver function tests every 3-6 months. • Advise the patient on the risk of pulmonary and hepatic fibrosis and the symptoms to report if they develop during treatment. Reactions can develop acutely or insidiously. • Advise the patient on the risk of peripheral and optic neuropathy and the symptoms to report if they develop during treatment.

Second-line antibiotic options on urology or infection specialist advice only

If resistance to first-line antibiotics and methenamine, used as single agents, is not tolerated or contra-indicated, other antibiotic agents may be considered after discussion with Urology and/or an Infection Specialist if the patient is not under urology. Broader spectrum agents such as cefalexin, ciprofloxacin and co-amoxiclav have a higher risk of *C. difficile* diarrhoea and selection for resistance, so they should not be routinely used for prophylaxis and be reviewed with a trial of stopping after 6 months. In addition, MHRA has issued an alert restricting the use of Fluoroquinolone antibiotics, e.g. ciprofloxacin.

Second-line antibiotic options on urology or infection specialist advice only. Trial of stopping after 6 months.

Antibiotic	Dose	Cautions and Monitoring
Cefalexin	500 mg one dose post-coital **or** 125 mg nightly	• Higher risk of selection for resistant infections • Higher risk of *C. difficile* infection
Pivmecillinam	200 mg one dose post-coital **or** 200 mg nightly	• Unknown safety profile and potential carnitine deficiency with prolonged use [10] Note the BNF pivmecillinam dosing for "chronic or recurrent bacteriuria" is not applicable for recurrent symptomatic urinary tract infections.

3. Managing 'breakthrough' UTIs on a continuous prophylactic agent

Methenamine prophylaxis

- The breakthrough infection should be treated according to culture and sensitivity results if available.
- Methenamine prophylaxis should be continued alongside the antibiotic course for the breakthrough infection if there has been a good response.
- If multiple breakthrough UTIs occur (≥2 UTIs in 6 months), methenamine should be stopped or changed to an alternative prophylactic agent (antibiotic).
- Consider referral to Urology at this point if not already been investigated.

Antibiotic prophylaxis

- The first breakthrough infection should be treated according to culture and sensitivity results if available, with the original prophylaxis being held and then restarted once the infection has resolved if the culture confirms susceptibility to the prophylactic agent.
- If the culture shows resistance to the prophylactic agent, or multiple breakthrough UTIs occur (≥2 UTIs in 6 months), prophylaxis has therefore proved ineffective and should be stopped or changed to an alternative prophylactic agent (antibiotic or methenamine).
- Consider referral to Urology at this point if you have not already been referred.

4. Managing a patient who has had a prolonged course of a continuous prophylactic agent:

Methenamine prophylaxis

Identifying patients for review:

- Patients should be reviewed after 6 months of prophylactic methenamine then every 12 months, or earlier if agreed with the person

If a patient starts to suffer from recurrent UTIs again and methenamine was effective previously, this can be restarted. Consider referral for investigation (if the patient has not already been investigated).

Antibiotic prophylaxis

Identifying patients for review:

- Patients should be reviewed after 6 months of prophylactic antibiotics with a view to stopping.
- 12 months is a suggested trigger for audit purposes for patients on long-term antibiotic prophylaxis.
- Patients who have urine cultures confirming resistance to the prophylactic agent they are on should have their prophylaxis stopped (exposure to antibiotic without benefit) and a clinical review to discuss ongoing management and/or the need for referral.

Stopping continuous prophylaxis:

It is understandable for patients to be anxious about a return to frequent UTIs after stopping continuous prophylaxis. However, a prolonged period of a prophylactic agent may allow bladder epithelial healing, reducing the risk of future UTIs when antibiotics are then stopped.

- The proportion of patients who will return to suffering recurrent UTIs after stopping continuous prophylaxis may be around 50%[7].
- This means a significant number of patients are able to stop continuous prophylaxis without a return of symptoms and therefore avoid the risks of resistance emerging and side-effects.
- One option is to provide 'standby' antibiotics when stopping continuous prophylaxis which may give sufficient reassurance to patients for a trial off prophylaxis.
- Consider referring patients who relapse after stopping continuous prophylaxis, if not already been investigated.
- Longer term prophylaxis with an antibiotic or methenamine may be helpful in those patients whose UTIs are suppressed when on prophylaxis and recur when prophylaxis is discontinued after 6 months.

Summary of Management of Recurrent Lower UTIs (in non-pregnant women, trans men and non-binary people with a female urinary system)

≥ 3 symptomatic lower UTIs / 12 months or
≥2 symptomatic lower UTIs / 6 months

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Consider red flag indications for Urology referral (see page 1)

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Advice on Conservative Measures (see page 2)

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Consider risks and benefits with the patient of:

1. **Vaginal Oestrogen**
2. **Single-dose Antibiotics (if sexual intercourse identified as trigger)**
3. **Trial of continuous prophylaxis (methenamine OR antibiotics 2nd line)**
4. **Stand-by Antibiotics (in certain cases, if appropriate)**

→ **For Single-dose or Stand-by antibiotics:**
Review repeat prescriptions at 6 months to assess benefit and if any resistant urine cultures

Choice dependent on factors outlined on page 4

Continuous methenamine prophylaxis
Trial of 6 months of methenamine (see page 3)

No breakthrough UTIs →

After 6 months, review prophylaxis
Around 50% will not return to recurrent symptoms.
Consider offering stand-by antibiotics if patient concerned.

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If recurrent UTIs return after stopping, restart methenamine and consider referral

Breakthrough UTI whilst on prophylaxis →

If ≥2 breakthrough UTIs:
Methenamine prophylaxis has failed and should be stopped or changed
Consider referral if not already investigated

Continuous antibiotic prophylaxis Trial of 6 months of nightly antibiotics (see page 3)

No breakthrough UTIs →

After 6 months, stop prophylaxis
Around 50% will not return to recurrent symptoms.
Consider offering stand-by antibiotics if patient concerned.

↓

If recurrent UTIs return after stopping, restart and consider referral

Breakthrough UTI whilst on prophylaxis →

If ≥2 breakthrough UTIs, or the urine cultures are resistant to the prophylactic agent:
Antibiotic prophylaxis has failed and should be stopped or changed
Consider referral if not already investigated

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